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| EXAMINER | |
|---|---|
| YAO, LEI | |

| ART UNIT | PAPER NUMBER |
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| 1642 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/014,887 | KRISSANSEN ET AL. | |
| | Examiner | Art Unit | |
| | Lei Yao, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,10-15,18-23,26-31,34-39 and 42-47* is/are pending in the application.

4a) Of the above claim(s) *10, 11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43,47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,12-14,20-22,28-30,36-38 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Request for Continued Examination

The request filed on 7/16/2007 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10014887 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 5-9, 16, 17, 24, 25, 32, 33, 40, 41, and 48-55 are cancelled. Claims 1-4, 10-15,18-23, 26-31, 34-39, and 42-47 are pending. Claims 10, 11, 15, 18, 19, 23, 26, 27, 31, 34, 35, 39, 42, 43, and 47 are withdrawn form consideration as non-elected invention. Claims 1-4, 12-14, 20-22, 28-30, 36-38, 44-46 are examined on the merits.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 28-30, 36-38, and 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 44-46 are indefinite because claims depend on non-existed claims, particularly, claims 44 and 46 depend on claim 61 and 62, which are not in the claim list. Claim 45 depends on claim 44. Thus, it is not clear the claimed limitation recited in the claims. Correction is required. In the interest of compact prosecution, the claims have been treated as if they depended from claims 4.

2. Claims 3, 4, 28-30, 36-38, and 44-46 are indefinite because

A) clause ".....comprises the step of administering to said patient when treated with said T-cell co-stimulatory cell adhesion molecule (CAM) an amount of a tumor growth-restricting agent, which is effective, in combination with the immunotherapeutic agent to eradicate any advanced or large tumors present in said patient..... in line 3-7 of base claim 3 is not clear. It is not clear what are comprised in the

treatment composition, CAM, and/or tumor growth restricting agent, in combination with immunotherapeutic agent? Clarification is required.

B) clause "....with said tumor growth-restricting agent an amount of a T-cell co-stimulatory cell adhesion molecule (CAM) which, upon subsequent administration of said tumor growth restricting agent, acts in combination with said tumor growth restricting agent to eradicate an advanced or large tumors present..." in line 3-7 of base claim 4. It is not clear what the method step is and what is comprised in the treatment composition. Clarification is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 12-14, 20-22, 28-30, 36-38, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Futami et al., (J of Immunotherapy, vol 12, 247-255, provided before) in view of Wilson et al., (Int. J. Radiation Oncology Biol. Phys., Vol. 42, page 905-908, 1998) and Olsson et al., (International Immunology, vol 10, page 499-506, provided before).

The claims are drawn to methods of treating a patient with advanced or large tumor comprising administering CAM (B7.1) in conjunction with tumor restricted agent DMXAA (claims 1 and 2) or potentiate the activity of tumor restricted agent DMXAA or CAM (B7.1) comprising administering CAM

(B7.1), CD80 antigen, or tumor restricted agent DMXXA (claims 3 and 4) in combination with immunotherapeutic agent to eradicate an advanced or large tumors present in a patient, wherein CAM is administered prior to from 12-48 hours the tumor restricted agent DMXXA (claims 12-13, 20-21, 28-29, 36-37, 44-45), wherein the method further includes the administering of an addition tumor growth-restricting agent (claims 14, 22, 30, 38, 46).

Futami et al., teach a method of treating tumor by 5-methyl XAA in conjunction with a T-cell stimulating molecule, IL-2. Futami et al., teach that the activities of XAA analogues can be potentiated by recombinant IL-2 in treating a tumor by showing the synergistic effect in combination (page 251, col 2). Futami et al., teach a method of treating cancer by administering a subject both reagents or administrating two reagent at different time (page 249, column 1-2 and page 251, column 1). Futami et al., also teach the analogues of XAA alone or IL-2 alone is not as effective as combined therapy for treating a mice bearing a tumor (figure 2-4).

Futami et al., do not teach that treating cancer with specific analogy of XAA, DMXAA (5, 6, dimethyal XAA) in conjunction with CAM, B7.1.

Wilson et al., teach a specific analogy of XAA, 5,6 dimethylmanthenone-4-acetic acid (DMXAA), potentiate tumor radiation response compared to each treatment alone (entire reference, especially, page 906, col 2, page 907, tables). Wilson et al., teach the treatment commenced established tumor when tumors reach to 0.4-0.6g (page 96, col line 5-8 from bottom). Wilson et al., also teach that DMXAA induces synthesis of TNF, an anti-tumor agent production (abstract).

Olsson et al., teach Human IL-2 is induced by CD80 (B7.1, a CAM molecule) in cancer cells and T cells (entire article).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the teachings of Wilson et al., and Olsson et al., to the method of Futami et al., in order to benefit for the treatment of advanced or large tumor because both Wilson et al., and Futami have already shown the advantage of the tumor therapy by potentiating or synergistic response for the large tumor in combination of anti-tumor treatment with DMXAA and because Olsson et al., show the association between T cell growth factor IL-2 and B7.1 stimulation. One of ordinary skill in the art at the time the

invention was made would have been motivated with reasonable expectation of success to modify the treatment schedule or method steps in order to optimize and increase the efficacy of the treatment by administering B7.1 prior to the DMXAA because Futami et al., have already shown administering a subject two or more reagents at different times and Olsson et al., teach that T-cell proliferation stimulated by IL-2 is induced by B7.1 and Wilson et al., also show that DMXAA induces other antitumor cytokine productions during the treatment, which would suggest the combination treatment results from more than two anti-tumor agents presented in the subject. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Response to applicant's argument related to the new ground rejection above.

The response filed 7/16/2007 has been carefully considered but is deemed not to be persuasive.

At page 15 of the remarks, applicant first agrees with the Examiner that increased IL-2 levels as a result of administration of CAM B7.1 and then argues:

> the reference concludes that CAM B7.1 stimulates IL-2 production only as a stepping stone to the actual conclusion of the reference, i.e., that, unlike CAM B7.2., CAM B7.1 is needed to induce a wide variety of transcription factors, thereby inducing IL-2, which stimulates vigorous T-cell proliferation.

And then at page 15-16 applicant argues:

> there is no motivation to combine Futami et al. and Olsson et al. because, specifically, Futami discusses Ia) the treatment of cancer with a combination of FAA derivatives and Ib) the single exogenously administered purified cytokine IL-2, while Olsson 2a) does not teach or discuss any form of cancer whatsoever but instead teaches T cell activation 2b) not resulting in the single exogenously administered purified cytokine IL-2, but instead producing a multiplicity of heterogeneous effects including T cell proliferation and production of multiple cytokines.
>
> nowhere in the specification is the mode of action of any of the disclosed CAMs given, nor is there any indication whatsoever that these CAMs are mediated via IL-2 activity. Similarly, Olsson does not discuss cancer at all, and clearly does not discuss any involvement of IL-2 in cancer treatment, much less IL-2 mediation of CAM B7.1 action in cancer treatment.

In response, first, Olsson et al., explicitly teach that CD80 (B7,1) is a strong inducer of IL-2 in T and tumor cells. For example, On page 503, column 2, line 6+ from bottom, Olsson et al., state "human CD4+ T cells responded to only marginally to TCR engagement by superantigen pressed by CHO-OR and that co-

stimulation with CD80 induced a profound IL-2 production and T-cell proliferation". On page 504, column 1, Olsson et al., state " both CD80 and CD86 costimulation induced IL-2 gene transcription, however, CD86 induces 2- or 3-fold lower level of transcription activity and IL-2 production compared to CD80". Finally Olsson et al., summarize the finding in the abstract stating that CD80 induced higher levels of IL-2 promoter-enhancer activity compared to CD86 (abstract, line 13+). Thus, Olsson et al., explicitly teach that IL-2 is produced in the presence of B7.1 in T cell as well as in tumor cells.

Second, claimed method is in vivo administration of DMXAA compound combined with B7.1 DNA to treat large tumor. The references by Futami et al. and Wilson et al., teach treating tumor with DMXAA in combination with IL-2, not with B7.1. However, Olsson et al. teach that IL-2, as a T-cell growth or activation factor is induced or increased when a tumor or T-cell transfected with B7.1. Thus, Olsson et al., make a strong suggestion that the method of Futami et al., could be performed by replacing the IL-2 protein with B7.1 DNA to produce endogenous IL-2 that could be more potent for the activation of T-cell for the tumor immunity. Accordingly one skilled in the art would be motivated to combine the teachings to use the method to treat a large tumor.

Third, the response to the previous argument set forth in the previous office action dated 1/16/2007 has been made record and again stated in MPEP 2141.02 (also see rejection above)

In determining the difference between the prior art and the claims, the question under 35 USC103 is not whether the difference themselves would have been obvious, but whether the claimed invention as a whole would have been obvious.

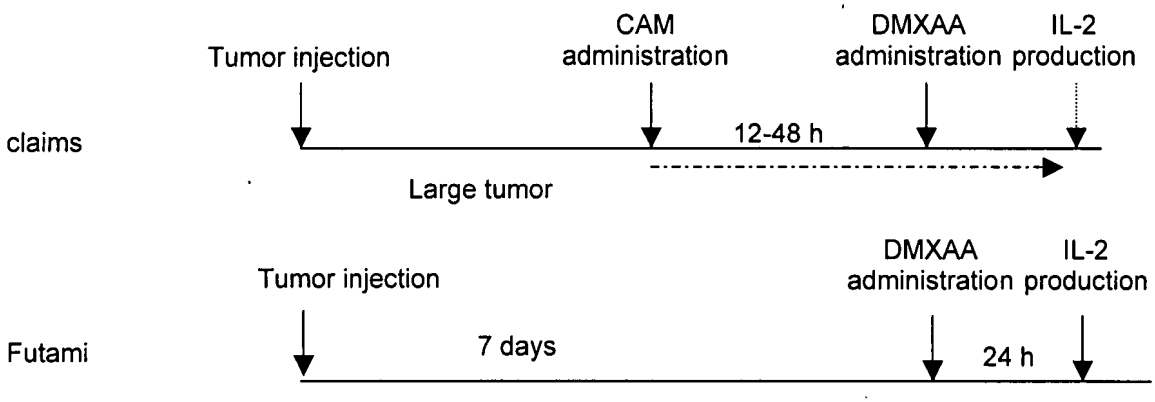
Because the amended claims are now reciting DMXAA as tumor restricted agent that is not taught by Futami et al., the Office adds another reference by Wilson et al., who teach treating cancer with DMXAA in combination with other treatment. Therefore, the combination of references by Futami et al., Wilson et al., and Olsson et al., teach every limitation as stated in the rejection above and would be prima facie obvious for one skilled in the art to combine all of them together because combining the anti-cancer agents to form a new protocol is routine for one skilled in the art to practice the cancer treatment. One of ordinary skill in the art at the time the invention was made would have been motivated with high expectation of success to modify the treatment schedule or method steps based on the teachings of the art. Therefore, claimed invention would be obvious over the references in combination.

At page 17-18, applicant further argue no treatment of large, advanced tumor burden taught by Futami et al., or Olsson et al. In response, Futami et al., on page 249, column 2, teach that treatment was initiated on day 7, which indicates certain tumor mass has been formed. In addition, in current rejection, the Office adds reference by Wilson et al., who teach "the treatment commenced established tumor when tumors reach to 0.4-0.6g" (see above in the rejection). Based on definition of the instant specification one skilled in the art and applicants would consider this size of the tumor as a large or advanced tumor mass.

Regarding with the method step of administering of the CAM 12-48 hours prior to the tumor-growth restricting agent, applicants argue:

> the limitation of timing of delivery of the compounds of the present invention is not taught or suggested in the combination of Futami et al. and Olsson et al.
> Futami teaches the administration of tumor growth- restricting agent fully 168 hours (7 days) before administration of IL-2, i.e., 168 hours before administration of what the Examiner claims is the desired product of the administration of CAM

In response, The Office disagree Applicant's interpretation of the teaching by Futami. First, Futami et al., teach that one day after XAA derivative administration, mice received the first injection of rIL-2. Since Olsson et al., teach IL-2 is induced by B7.1. It would arrive current invention by given B7.1 prior to DMXAA, thus, IL-2 is timely produced after DMXAA is administered. Time line for the administering is schematically described below:



Therefore, one skilled in the art would be motivated with reasonable expectation of success to use current invention to treat large tumor by given CAM, B7.1, prior to DMXAA because skilled artisan clearly knows that protein production from a DNA requires more than 12 hours. Thus, applicant's argument has not been found persuasive and the rejection is made again above.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

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